COVENANT AEGIS REVIEW OF CLINICAL INTELLIGENCE VOL. 7 · NO. 3 · 2026 · PP. 12–32

Longevity Medicine: Targeting the Hallmarks of Aging to Extend Healthspan

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Received 18 Jan 2026 · Revised 6 Mar 2026 · Accepted 15 Mar 2026 · REVIEW ARTICLE · DOI 10.48-CA/clinint.2026.0303 ·
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ABSTRACT

Background. Ageing is the dominant risk factor for most chronic disease; the geroscience hypothesis holds that targeting fundamental ageing processes could delay multiple diseases simultaneously. **Objective.** To review the molecular hallmarks of ageing, the experimental evidence for candidate interventions, and the biomarkers and trial designs required to translate geroscience into clinical longevity medicine. **Methods.** Narrative synthesis of preclinical and clinical literature (2009–2025), grading evidence from invertebrate models to human trials. **Results.** Rapamycin extends median lifespan ~9–14% in genetically heterogeneous mice even when started late; senolytic clearance delays multiple pathologies; epigenetic clocks predict morbidity and mortality beyond chronological age. Human evidence remains early, dominated by surrogate endpoints. **Conclusion.** Geroscience provides a credible mechanistic basis for extending healthspan, but rigorous human trials with validated ageing biomarkers—exemplified by the TAME design—are the translational priority over premature commercialisation.

Keywords: geroscience; hallmarks of aging; healthspan; senolytics; rapamycin; epigenetic clock; biological age

1. Introduction

Ageing is the dominant risk factor for cardiovascular disease, cancer, neurodegeneration and metabolic disorders. The geroscience hypothesis holds that by slowing the biological processes of ageing it may be possible to delay multiple age-related diseases at once, compressing morbidity into a shorter terminal period [1]. Longevity medicine translates this hypothesis into a clinical discipline focused on extending *healthspan*—life free of significant disease—rather than lifespan alone.

2. The Hallmarks of Aging

López-Otín and colleagues organised the molecular drivers of ageing into an influential set of hallmarks, updated in 2023 to twelve interconnected processes [2]. Each is, in principle, a therapeutic target; their interdependence means that

intervening on one (e.g., senescence) can modulate others (e.g., inflammation).

Table 1. The twelve hallmarks of ageing and representative interventions [2].

Hallmark	Candidate lever
Genomic instability	DNA-repair support
Telomere attrition	Telomerase modulation
Epigenetic alterations	Partial reprogramming
Loss of proteostasis	Chaperone induction
Disabled macroautophagy	Autophagy inducers
Deregulated nutrient sensing	mTOR/AMPK modulation
Mitochondrial dysfunction	NAD+ precursors
Cellular senescence	Senolytics
Stem-cell exhaustion	Regenerative therapy
Altered communication	Anti-inflammatories
Chronic inflammation	Senomorphics
Dysbiosis	Microbiome modulation

3. Interventions and Evidence

3.1 Nutrient-Sensing Pathways

Inhibition of the mTOR pathway with rapamycin extends lifespan in genetically heterogeneous mice, even when started late in life [3]. Caloric restriction reliably extends lifespan across model organisms and improves metabolic markers in humans [4]. Metformin shows geroprotective signals and underlies a proposed clinical trial [5].

3.2 Cellular Senescence

Senescent cells accumulate with age and secrete pro-inflammatory factors. Their clearance in mice delays multiple age-related pathologies and extends median lifespan [6]; senolytic combinations such as dasatinib plus quercetin reduce senescent-cell burden in early human studies [7].

3.3 Partial Reprogramming

Transient expression of reprogramming factors can reverse cellular markers of ageing and restore tissue function in mice without inducing tumours, suggesting epigenetic ageing is partly reversible [8].

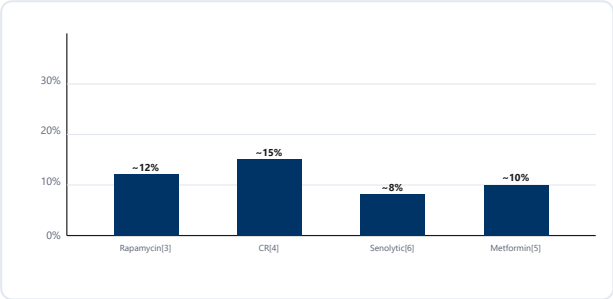


Figure 1. Approximate median-lifespan extension reported in murine studies for representative interventions [3–6]. Magnitudes vary by strain, sex, dose and onset; values are indicative and not directly comparable. Human lifespan effects are *not* established.

4. Measuring Biological Age

Progress depends on biomarkers that track ageing faster than survival. DNA-methylation "epigenetic clocks" estimate biological age and predict morbidity and mortality beyond chronological age [9]. Composite measures integrating clinical chemistries also predict outcomes and can serve as surrogate endpoints once prospectively validated [10]. Figure 2 illustrates the conceptual divergence between chronological and biological age that such clocks aim to quantify.

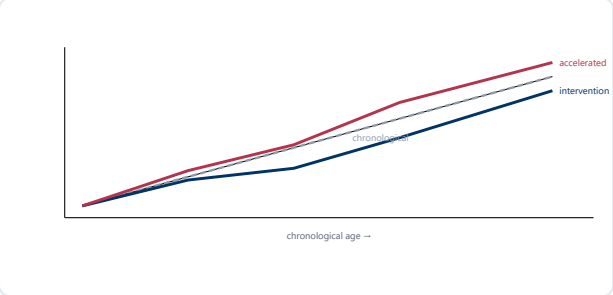


Figure 2. Schematic: biological age (epigenetic/biomarker estimate) may diverge above (accelerated) or below (intervention) the chronological line. Conceptual illustration of the construct measured by validated clocks [9,10].

5. Translation and Trial Design

The Targeting Aging with Metformin (TAME) trial is designed to test whether an ageing-directed intervention delays a composite of age-related diseases, establishing a regulatory pathway for treating ageing as an indication [5]. Responsible longevity medicine requires randomised evidence, validated surrogate endpoints, and caution against marketing unproven interventions directly to consumers.

6. The Covenant Aegis Longevity Program

Our program is measurement-driven: each plan is anchored in validated biomarkers of biological age, graded by strength of evidence, and limited to interventions with acceptable safety profiles. Lifestyle optimisation—exercise, nutrition, sleep and metabolic control—remains the evidence-backed foundation, with investigational agents offered only within monitored, consented protocols.

7. Discussion and Limitations

The chasm between robust preclinical data and sparse human evidence is the field's defining limitation. Surrogate-endpoint validity, long time-horizons, heterogeneity of ageing, and a commercial environment prone to overclaiming all demand restraint. Figures here are conceptual; no human lifespan-extension claim is supported by current evidence.

8. Conclusion

Geroscience provides a credible mechanistic basis for extending healthspan, and several interventions show strong preclinical and early clinical promise. The translational priority is rigorous human trials with validated ageing biomarkers, not premature commercialisation.

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9. Mechanistic Deep-Dive: Nutrient Sensing

The mechanistic-target-of-rapamycin (mTOR) pathway integrates nutrient and growth signals; its inhibition extends lifespan across yeast, worms, flies and mice, making it the most reproducible pharmacological lever in geroscience [A1]. AMP-activated protein kinase (AMPK) and sirtuins act as complementary energy sensors, and caloric restriction converges on these pathways. The interventions in Section 3 can thus be read as different entry points into a shared nutrient-sensing network, which explains both their overlapping benefits and the risk of redundant or antagonistic combinations.

Table A1. Geroprotective interventions: pathway, strongest model evidence and human status.

Intervention	Pathway	Human status
Rapamycin	mTOR	Early trials
Metformin	AMPK	Trial proposed (TAME)
Caloric restriction	mTOR/AMPK	CALERIE evidence
Senolytics (D+Q)	Senescence	Pilot trials
NAD+ precursors	Mitochondria	Mixed early data

10. Human Evidence: CALERIE and Beyond

The CALERIE randomised trial demonstrated that sustained caloric restriction in non-obese adults is feasible and improves cardiometabolic risk markers and a composite measure of biological-aging pace [A2]. This is among the strongest human data linking a geroscience intervention to a validated aging biomarker. By contrast, NAD+-precursor supplements show inconsistent clinical benefit despite raising NAD+ levels, illustrating that target engagement does not guarantee a healthspan effect [A3].

11. Biomarkers of Aging

Second- and third-generation epigenetic clocks (e.g., PhenoAge, GrimAge, DunedinPACE) predict morbidity and mortality beyond chronological age and are increasingly used as surrogate endpoints [A4,A5]. Composite phenotypic measures integrate standard clinical chemistries. Figure A1 contrasts the predictive validity of clock generations. No biomarker is yet a regulator-accepted surrogate, which is the central translational bottleneck.

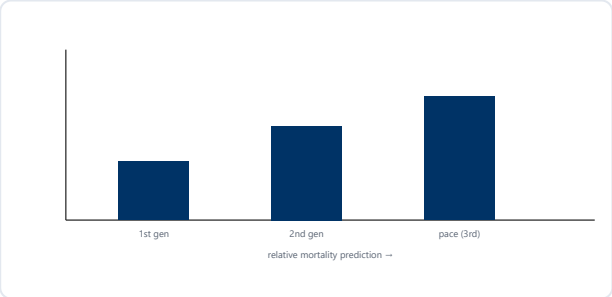


Figure A1. Schematic relative mortality-prediction strength across epigenetic-clock generations; later clocks trained on health outcomes outperform first-generation age predictors [A4,A5]. Conceptual.

12. Safety and Risk–Benefit

Geroprotective agents are candidate *preventives* given to largely healthy people

over long periods, so the safety bar is high. Rapamycin causes immunosuppression and metabolic effects at transplant doses; intermittent low-dose regimens are under study to separate geroprotection from toxicity [A1]. Senolytics are given intermittently ("hit-and-run") to limit exposure. The asymmetry between speculative long-term benefit and concrete near-term risk mandates conservative, monitored protocols and rejection of direct-to-consumer hype.

13. Ethical and Societal Considerations

Extending healthspan raises questions of access and equity, the distinction between treating disease and enhancing the healthy, and the integrity of an unregulated longevity marketplace. Responsible practice separates evidence-based lifestyle and risk-factor management—well supported and broadly accessible—from investigational interventions confined to trials.

14. Trial Design for Aging

The TAME framework proposes a composite endpoint of multiple age-related diseases to test whether an intervention delays the onset of age-related morbidity as a whole, and to establish aging as a treatable indication with regulators [A6]. Surrogate-endpoint validation, long follow-up and large samples are the practical hurdles; biomarker-anchored adaptive designs are an active area.

15. Future Directions

Partial epigenetic reprogramming, targeted senolytics, and combination regimens guided by validated biomarkers are the most promising avenues. The decisive need is rigorous human trials with regulator-accepted aging surrogates; until then, the evidence-based core of longevity medicine remains exercise, nutrition, sleep, and metabolic and cardiovascular risk control.

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Author contributions: KN conceived the review; ER and FA performed evidence grading; RAM supervised. All authors revised. **Funding:** Covenant Aegis HealthTech Division. **Competing interests:** Authors are affiliated with Covenant Aegis.

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